

LISTING OF THE CLAIMS

1. (Previously presented) A method of identifying a compound that modulates nuclear receptor activity, the method comprising:
modeling a test compound that fits spatially into the nuclear receptor ligand binding domain using an atomic structural model of a portion of the estrogen receptor α ligand binding domain, wherein said atomic structural model comprises atomic coordinates of helix 12 of the ligand binding domain, and of a coactivator binding site, and further comprises atomic coordinates of a coactivator bound to the coactivator binding site; and
screening said test compound in an assay characterized by binding of a test compound to the ligand binding domain, thereby
identifying a test compound that modulates nuclear receptor activity.
2. (Previously presented) The method of Claim 1 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu 428, Gly 521, His524, Leu525 and Met528, and wherein said test compound interacts with at least one of said amino acid residues.
3. (Original) The method of Claim 1 wherein the test compound is an agonist and nuclear receptor activity is measured by binding of a coactivator to the coactivator binding site.
4. (Previously presented) The method of Claim 1 wherein the test compound is an antagonist and nuclear receptor activity is measured by a change in position of helix 12 so that helix 12 contacts the coactivator binding site thereby inhibiting coactivator binding.
5. (Previously presented) The method of Claim 1 wherein the test compound is an antagonist and nuclear receptor activity is measured by blocking of coactivator binding.
6. (Original) The method of Claim 1 wherein said screening is in vitro.

7. (Original) The method of Claim 6 wherein said screening is high throughput screening.
8. (Original) The method of Claim 1 wherein said test compound is from a library of compounds.
9. (Previously presented) The method of Claim 1 wherein said test compound is a small organic molecule, a peptide, or a peptidomimetic.
10. (Previously presented) The method of Claim 1 wherein the modeling comprises providing the atomic coordinates of the portion of the estrogen receptor α ligand binding domain to a computerized modeling system.
11. (Original) The method of Claim 1 wherein said nuclear receptor is selected from the group consisting of estrogen receptors, thyroid receptors, retinoid receptors, glucocorticoid receptors, progesterin receptors, mineralocorticoid receptors, androgen receptors, peroxisome receptors and vitamin D receptors.
12. (Original) The method of Claim 11 wherein said nuclear receptor is an estrogen receptor.
13. (Original) The method of Claim 12 wherein said estrogen receptor is the estrogen receptor α .
14. (Previously presented) A method of identifying a compound that modulates ligand binding to a nuclear receptor, the method comprising:
 - modeling a test compound that fits spatially into the nuclear receptor ligand binding domain using an atomic structural model of a portion of the estrogen receptor α ligand binding domain, wherein the atomic structural model comprises atomic coordinates of helix 12 of the ligand binding domain, and of a coactivator binding site, and further comprises atomic coordinates of a coactivator bound to the coactivator binding site; and
 - screening said test compound in an assay characterized by binding of the test compound to the ligand binding domain, thereby

identifying a test compound that modulates ligand binding to said nuclear receptor.

15. (Previously presented) The method of Claim 14 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu 428, Gly 521, His524, Leu525 and Met528, and wherein said test compound interacts with at least one of said amino acid residues.
16. (Original) The method of Claim 14 wherein said nuclear receptor is selected from the group consisting of estrogen receptors, thyroid receptors, retinoid receptors, glucocorticoid receptors, progestin receptors, mineralocorticoid receptors, androgen receptors, peroxisome receptors and vitamin D receptors.
17. (Original) The method of Claim 16 wherein said nuclear receptor is an estrogen receptor.
18. (Original) The method of Claim 17 wherein said estrogen receptor is the estrogen receptor α .
19. (Original) The method of Claim 14 wherein said screening is in vitro.
20. (Original) The method of Claim 19 wherein said screening is high throughput screening.
21. (Original) The method of Claim 14 wherein said test compound is from a library of compounds.
22. (Previously presented) The method of Claim 14 wherein said test compound is an agonist of ligand binding that facilitates binding of a coactivator to the coactivator binding site.
23. (Previously presented) The method of Claim 14 wherein said test compound is a small organic molecule, a peptide, or a peptidomimetic.

24. (Previously presented) A method for identifying an agonist of ligand binding to an estrogen receptor the method comprising:

modeling a test compound which fits spatially into an atomic structural model of the estrogen receptor α ligand binding domain, wherein the atomic structural model comprises atomic coordinates of helix 12 of the ligand binding domain, and of a coactivator binding site, and further comprises atomic coordinates of a coactivator bound to the coactivator binding site; and

screening in an assay for estrogen receptor activity a compound which increases the activity of the estrogen receptor by binding the ligand binding domain of the estrogen receptor, thereby identifying an agonist of ligand binding.

25. (Previously presented) The method of Claim 24 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528, and wherein said test compound interacts with at least one of said amino acid residues.

26 – 28. (Cancelled).

29. (Previously presented) A method of modulating nuclear receptor activity in a mammal by administering to a mammal in need thereof a sufficient amount of a compound that fits spatially and preferentially into a ligand binding domain of the nuclear receptor, wherein said compound is designed by a computational method that involves fitting an atomic model of the compound into an atomic structural model of the ligand binding domain of the estrogen receptor that comprises atomic coordinates of helix 12 of the ligand binding domain, and of a coactivator binding site, and further comprises atomic coordinates of a coactivator bound to the coactivator binding site, so that the molecule interacts with at least one amino acid residue corresponding to residues of human estrogen receptor α Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528.

30. (Previously presented) The method of Claim 29 wherein the test compound is an antagonist that causes a change in position of helix 12 so that helix 12 contacts the coactivator binding site thereby inhibiting coactivator binding.

31. (Original) The method of Claim 29 wherein said nuclear receptor is selected from the group consisting of estrogen receptors, thyroid receptors, retinoid receptors, glucocorticoid receptors, progestin receptors, mineralocorticoid receptors, androgen receptors, peroxisome receptors and vitamin D receptors.

32. (Original) The method of Claim 31 wherein said nuclear receptor is an estrogen receptor.

33. (Original) The method of Claim 32 wherein said estrogen receptor is the estrogen receptor α .

34. (Previously presented) A machine-readable data storage medium encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional representation of a molecular complex, wherein the data comprises coordinates of: a portion of an estrogen receptor ligand binding domain, including helix 12 of the ligand binding domain; a coactivator binding site; and a compound bound to the estrogen receptor coactivator binding site.

35. (Previously presented) The machine-readable data storage medium of Claim 34 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528.

36 – 38. (Cancelled)

39. (Previously presented) The machine-readable data storage medium of Claim 34 wherein said molecular complex is defined by the set of structure coordinates depicted in Appendix 1, or a homologue of said molecular complex, said homologue having a root mean square deviation from the coordinates of the backbone atoms of said ligand binding domain of not more than 1.5Å.

40. (Original) A machine-readable data storage medium comprising a data storage material encoded with a first set of machine readable data which, when combined with a

second set of machine readable data, using a machine programmed with instructions for using said first set of data and said second set of data, can determine at least a portion of the structure coordinates corresponding to the second set of machine readable data, wherein: said first set of data comprises a Fourier transform of at least a portion of the structural coordinates selected from the group consisting of coordinates depicted in Appendix 1 or Appendix 2; and said second set of data comprises an X-ray diffraction pattern of a molecule or molecular complex.

41. (Previously presented) The machine-readable data storage medium of Claim 40 wherein said nuclear receptor is selected from the group consisting of estrogen receptors, thyroid receptors, retinoid receptors, glucocorticoid receptors, progestin receptors, mineralocorticoid receptors, androgen receptors, peroxisome receptors and vitamin D receptors.

42. (Original) The machine-readable data storage medium of Claim 41 wherein said nuclear receptor is an estrogen receptor.

43. (Original) The machine-readable data storage medium of Claim 42 wherein said estrogen receptor is the estrogen receptor α .

44. (Previously presented) A cocrystal comprising: a portion of an estrogen receptor ligand binding domain; an agonist bound to the ligand binding domain; and a molecule bound to a coactivator binding site of the estrogen receptor.

45. (Currently amended) The cocrystal of Claim 44 wherein said ~~nuclear~~ estrogen receptor is ~~[[the]]~~ estrogen receptor α .

46. (Original) The cocrystal of Claim 45 wherein said estrogen receptor α is human.

47. (Currently amended) The cocrystal of Claim ~~[[46]]~~ 44 wherein said molecule is a peptide.

48. (Original) The cocrystal of Claim 47 wherein said peptide comprises a NR-box amino acid sequence or derivative thereof.

49. (Previously presented) A cocrystal comprising: a portion of an estrogen receptor ligand binding domain and an antagonist bound to the ligand binding domain, wherein said cocrystal diffracts with at least 1.9Å resolution.
50. (Previously presented) The cocrystal of Claim 44 wherein said cocrystal diffracts with at least 2.03 Å resolution.
51. (Currently amended) The cocrystal of Claim ~~[[50]]~~ 49 wherein said estrogen receptor is human.
52. (Previously presented) A computational method of designing a nuclear receptor ligand, comprising:
fitting an atomic model of the ligand into an atomic structural model of the ligand binding domain of the estrogen receptor, wherein the atomic structural model comprises atomic coordinates of helix 12 of the ligand binding domain, and of a coactivator binding site, and further comprises atomic coordinates of a coactivator bound to the coactivator binding site; and
carrying out a chemical modification of a first chemical moiety of said ligand that interacts with the ligand binding domain, to produce a second chemical moiety.
53. (Previously presented) The method of Claim 52 wherein the atomic structural model additionally comprises coordinates of at least one amino acid residue that corresponds to human estrogen receptor α residues Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528, and wherein said first chemical moiety interacts with at least one of said amino acid residues.
54. (Previously presented) The method of Claim 52 further comprising determining a change in interaction between said interacting amino acid and said ligand after the chemical modification of said first chemical moiety.
55. (Previously presented) The method of Claim 54 wherein said chemical modification enhances an interaction selected from the group consisting of: hydrogen bonding interaction, charge interaction, hydrophobic interaction, van der Waals interaction or dipole interaction

between said second chemical moiety and one of said amino acid residues compared to said first chemical moiety.

56. (Previously presented) The method of Claim 54 wherein said chemical modification reduces an interaction selected from the group consisting of: hydrogen bonding interaction, charge interaction, hydrophobic interaction, van der Waals interaction or dipole interaction between said second chemical moiety and one of said amino acid residues compared to said first chemical moiety.

57. (Original) The method of Claim 52 wherein said nuclear receptor is selected from the group consisting of estrogen receptors, thyroid receptors, retinoid receptors, glucocorticoid receptors, progestin receptors, mineralocorticoid receptors, androgen receptors, peroxisome receptors and vitamin D receptors.

58. (Original) The method of Claim 57 wherein said nuclear receptor is an estrogen receptor.

59. (Previously presented) The method of Claim 57 wherein the estrogen receptor is the estrogen receptor α .

60. (Original) The method of Claim 59 wherein the ligand is an agonist.

61. (Original) The method of Claim 60 wherein the ligand is selected from the group consisting of 17β -estradiol, diethylstilbestrol, moxestrol, mesohexestrol, coumestrol, Δ^9 -THC, o,p-DDT, zearalenone and kepone.

62. (Original) The method of Claim 61 wherein the ligand is 17β -estradiol, and the first chemical moiety is a free carbon of the A' ring located at a position selected from the group consisting of C6 α , C7 α , C12 α , C15 α , C16 α and C17 α .

63. (Original) The method of Claim 59 wherein the ligand is an antagonist.

64. (Original) The method of Claim 63 wherein the ligand is selected from the group consisting of ICI 164,384 and EM800.

65. (Original) The method of Claim 59 wherein the ligand is a selective estrogen receptor modulator.

66. (Original) The method of Claim 65 wherein the ligand is selected from the group consisting of tamoxifen, raloxifene and GW5638.

67. (Previously presented) A method of modulating nuclear receptor activity in a mammal by administering to a mammal in need thereof a sufficient amount of a ligand that fits spatially and preferentially into a ligand binding domain of a nuclear receptor of interest, wherein said ligand is designed by a computational method comprising:

fitting an atomic model of the ligand into an atomic structural model of the ligand binding domain of the estrogen receptor, wherein the atomic structural model comprises atomic coordinates of helix 12 of the ligand binding domain, and of a coactivator binding site, and further comprises atomic coordinates of a coactivator bound to the coactivator binding site; and
carrying out a chemical modification of a first chemical moiety of said ligand that interacts with the ligand binding domain, to produce a second chemical moiety.

68. (Previously presented) The method of Claim 67 wherein the atomic structural model additionally comprises coordinates of at least one amino acid residue that corresponds to human estrogen receptor α residues Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528, and wherein said first chemical moiety interacts with at least one of said amino acid residues.

69. (Original) The method of Claim 67 wherein said ligand is an antagonist.

70. (Original) The method of Claim 67 wherein said ligand is an agonist.

71. (Previously presented) The method of Claim 70 further comprising administering a coactivator mimic designed by a computational method that comprises: fitting an atomic model of the mimic into the atomic structural model where at least one amino acid residue of the nuclear receptor coactivator binding site that corresponds to human estrogen receptor α helix 3 residues Leu354, Val355, Met357, Ile358, Ala361 and Lys362, helix 4 residue Phe367, helix 5 residues Gln375, Val376, Leu379 and Glu380, helix 6 residue Trp383, and

helix 12 residues Asp538, Leu539, Glu542, Met543 and Leu544, interacts with at least one first chemical moiety of said coactivator mimic; and selecting at least one chemical modification of said first chemical moiety to produce a second chemical moiety that has a structure to either decrease or increase an interaction between said coactivator binding site and said second chemical moiety compared to an interaction between said coactivator binding site and said first chemical moiety.

72. (Previously presented) The method of claim 1 wherein the test compound is an antagonist that permits helix 12 to bind to a static region of the coactivator binding site.

73. (Previously presented) The method of claim 1 wherein the atomic structural model has coordinates presented in Appendix 1.

74. (Previously presented) The method of claim 1 wherein the atomic structural model is of a homolog of the portion of the estrogen α receptor ligand binding domain, wherein the homolog comprises a ligand binding domain that has a root mean square deviation of not more than 1.5 Å from the backbone atoms of the amino acid residues of the atomic structural model of Appendix 1.

75. (Previously presented) The method of Claim 1 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Ala350, Glu353, Leu387, Leu391, Arg394, and Phe404, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an agonist that interacts with at least one of said amino acid residues.

76. (Previously presented) The method of Claim 1 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Gly 521, His524, Leu525, and either residues Met421 and Met528, or residues Met388 and Ile424, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an agonist that interacts with at least one of said amino acid residues.

77. (Previously presented) The method of Claim 1 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen

receptor α residues Met343, Leu346, Thr347, Ala350, Trp383, Leu384, Leu387, and Leu525, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an antagonist that interacts with at least one of said amino acid residues.

78. (Previously presented) The method of Claim 1 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Met421, Ile 424, Gly 521, His524, and Leu525, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an antagonist that interacts with at least one of said amino acid residues.

79. (Previously presented) The method of claim 1 wherein the atomic structural model is experimentally derived.

80. (Previously presented) The method of claim 79 wherein the atomic structural model has a resolution of at least 2.03 Å.

81. (Previously presented) The method of claim 4 wherein the modeling further comprises comparing a second atomic structural model of a portion of the estrogen receptor α ligand binding domain with the atomic structural model, wherein the second atomic structural model comprises atomic coordinates of amino acid residues of helix 12 of the ligand binding domain and of a coactivator binding site, wherein the helix 12 contacts the coactivator binding site, and further comprises atomic coordinates of an antagonist molecule bound to the ligand binding domain.

82. (Previously presented) The method of claim 81 wherein the second atomic structural model is experimentally derived.

83. (Previously presented) The method of claim 82 wherein the second atomic structural model has a resolution of at least 1.90 Å.

84. (Previously presented) The method of claim 81 wherein the second atomic structural model has coordinates presented in Appendix 2.

85. (Previously presented) The method of claim 81 wherein the second atomic structural model is of a homolog of the portion of the estrogen α receptor ligand binding domain, wherein the homolog comprises a ligand binding domain that has a root mean square deviation of not more than 1.5 Å from the backbone atoms of the amino acid residues of the atomic structural model of Appendix 2.
86. (Previously presented) The method of Claim 14 wherein the test compound is an antagonist that permits helix 12 to bind to a static region of the coactivator binding site.
87. (Previously presented) The method of claim 14 wherein the atomic structural model has coordinates presented in Appendix 1.
88. (Previously presented) The method of claim 14 wherein the atomic structural model is of a homolog of the portion of the estrogen α receptor ligand binding domain, wherein the homolog comprises a ligand binding domain that has a root mean square deviation of not more than 1.5 Å from the backbone atoms of the amino acid residues of the atomic structural model of Appendix 1.
89. (Previously presented) The method of Claim 14 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Ala350, Glu353, Leu387, Leu391, Arg394, and Phe404, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an agonist that interacts with at least one of said amino acid residues.
90. (Previously presented) The method of Claim 14 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Gly 521, His524, Leu525, and either residues Met421 and Met528, or residues Met388 and Ile424, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an agonist that interacts with at least one of said amino acid residues.
91. (Previously presented) The method of Claim 14 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Thr347, Ala350, Trp383, Leu384, Leu387, and Leu525,

wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an antagonist that interacts with at least one of said amino acid residues.

92. (Previously presented) The method of Claim 14 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Met421, Ile 424, Gly 521, His524, and Leu525, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an antagonist that interacts with at least one of said amino acid residues.

93. (Previously presented) The method of Claim 14 wherein the modeling comprises providing the atomic coordinates of the portion of the estrogen receptor α ligand binding domain to a computerized modeling system.

94. (Previously presented) The method of claim 14 wherein the atomic structural model is experimentally derived.

95. (Previously presented) The method of claim 94 wherein the atomic structural model has a resolution of at least 2.03 Å.

96. (Previously presented) The method of Claim 14 wherein the test compound is an antagonist that causes a change in position of helix 12 so that helix 12 contacts the coactivator binding site thereby inhibiting coactivator binding.

97. (Previously presented) The method of claim 96 wherein the modeling further comprises comparing a second atomic structural model of a portion of the estrogen receptor α ligand binding domain with the atomic structural model, wherein the second atomic structural model comprises atomic coordinates of amino acid residues of helix 12 of the ligand binding domain and of a coactivator binding site, wherein the helix 12 contacts the coactivator binding site, and further comprises atomic coordinates of an antagonist molecule bound to the ligand binding domain.

98. (Previously presented) The method of claim 97 wherein the second atomic structural model is experimentally derived.
99. (Previously presented) The method of claim 98 wherein the second atomic structural model has a resolution of at least 1.90 Å.
100. (Previously presented) The method of claim 97 wherein the second atomic structural model has coordinates presented in Appendix 2.
101. (Previously presented) The method of claim 97 wherein the second atomic structural model is of a homolog of the portion of the estrogen α receptor ligand binding domain, wherein the homolog comprises a ligand binding domain that has a root mean square deviation of not more than 1.5 Å from the backbone atoms of the amino acid residues of the atomic structural model of Appendix 2.
102. (Previously presented) The method of Claim 24 wherein said screening is in vitro.
103. (Previously presented) The method of Claim 102 wherein said screening is high throughput screening.
104. (Previously presented) The method of Claim 24 wherein said test compound is from a library of compounds.
105. (Previously presented) The method of Claim 24 wherein said test compound facilitates binding of a coactivator to the coactivator binding site.
106. (Previously presented) The method of Claim 24 wherein said test compound is a small organic molecule, a peptide, or peptidomimetic.
107. (Previously presented) The method of Claim 24 wherein the test compound is an agonist that permits the coactivator molecule to bind to a static region of the coactivator binding site.

108. (Previously presented) The method of Claim 24 wherein the modeling comprises providing the atomic coordinates of the portion of the estrogen receptor α ligand binding domain to a computerized modeling system.
109. (Previously presented) The method of Claim 24 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Ala350, Glu353, Leu387, Leu391, Arg394, and Phe404, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an agonist that interacts with at least one of said amino acid residues.
110. (Previously presented) The method of Claim 24 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Gly 521, His524, Leu525, and either residues Met421 and Met528, or residues Met388 and Ile424, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an agonist that interacts with at least one of said amino acid residues.
111. (Previously presented) The method of claim 24 wherein the atomic structural model is experimentally derived.
112. (Previously presented) The method of claim 111 wherein the atomic structural model has a resolution of at least 2.03 Å.
113. (Previously presented) The method of claim 24 wherein the atomic structural model has coordinates presented in Appendix 1.
114. (Previously presented) The method of claim 24 wherein the atomic structural model is of a homolog of the portion of the estrogen α receptor ligand binding domain, wherein the homolog comprises a ligand binding domain that has a root mean square deviation of not more than 1.5 Å from the backbone atoms of the amino acid residues of the atomic structural model of Appendix 1.
115. (Previously presented) A method for identifying an antagonist of ligand binding to an estrogen receptor, the method comprising:

modeling a test compound which fits spatially into an atomic structural model of the estrogen receptor α ligand binding domain, wherein the atomic structural model comprises atomic coordinates of helix 12 of the ligand binding domain, and atomic coordinates of a coactivator binding site, and further comprises atomic coordinates of a coactivator bound to the coactivator binding site; and screening in an assay for estrogen receptor activity a compound which decreases the activity of the estrogen receptor by binding the ligand binding domain of the estrogen receptor, thereby identifying an agonist of ligand binding.

116. (Previously presented) The method of Claim 115 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528, and wherein said test compound interacts with at least one of said amino acid residues.

117. (Previously presented) The method of Claim 115 wherein said screening is in vitro.

118. (Previously presented) The method of Claim 117 wherein said screening is high throughput screening.

119. (Previously presented) The method of Claim 115 wherein said test compound is from a library of compounds.

120. (Previously presented) The method of Claim 115 wherein the test compound is an antagonist that causes a change in position of helix 12 so that helix 12 contacts the coactivator binding site thereby inhibiting coactivator binding.

121. (Previously presented) The method of Claim 115 wherein the test compound is an antagonist that permits helix 12 to bind to a static region of the coactivator binding site.

122. (Previously presented) The method of Claim 115 wherein the modeling comprises providing the atomic coordinates of the portion of the estrogen receptor α ligand binding domain to a computerized modeling system.

123. (Previously presented) The method of Claim 115 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Thr347, Ala350, Trp383, Leu384, Leu387, and Leu525, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an antagonist that interacts with at least one of said amino acid residues.

124. (Previously presented) The method of Claim 115 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Met421, Ile 424, Gly 521, His524, and Leu525, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an antagonist that interacts with at least one of said amino acid residues.

125. (Previously presented) The method of claim 115 wherein the atomic structural model is experimentally derived.

126. (Previously presented) The method of claim 125 wherein the atomic structural model has a resolution of at least 2.03 Å.

127. (Previously presented) The method of claim 115 wherein the atomic structural model has coordinates presented in Appendix 1.

128. (Previously presented) The method of claim 115 wherein the atomic structural model is of a homolog of the portion of the estrogen α receptor ligand binding domain, wherein the homolog comprises a ligand binding domain that has a root mean square deviation of not more than 1.5 Å from the backbone atoms of the amino acid residues of the atomic structural model of Appendix 1.

129. (Previously presented) The method of claim 115 wherein the modeling further comprises comparing a second atomic structural model of a portion of the estrogen receptor α ligand binding domain with the atomic structural model, wherein the second atomic structural model comprises atomic coordinates of amino acid residues of helix 12 of the ligand binding domain and of a coactivator binding site, wherein the helix 12 contacts the coactivator

binding site, and further comprises atomic coordinates of an antagonist molecule bound to the ligand binding domain.

130. (Previously presented) The method of claim 129 wherein the second atomic structural model is experimentally derived.

131. (Previously presented) The method of claim 130 wherein the second atomic structural model has a resolution of at least 1.90 Å.

132. (Previously presented) The method of claim 129 wherein the second atomic structural model has coordinates presented in Appendix 2.

133. (Previously presented) The method of claim 129 wherein the second atomic structural model is of a homolog of the portion of the estrogen α receptor ligand binding domain, wherein the homolog comprises a ligand binding domain that has a root mean square deviation of not more than 1.5 Å from the backbone atoms of the amino acid residues of the atomic structural model of Appendix 2.

134. (Previously presented) A method of modulating estrogen receptor activity in a mammal by administering to a mammal in need thereof a sufficient amount of a compound that fits spatially and preferentially into an atomic structural model of a ligand binding domain of the estrogen receptor wherein said compound is designed so that binding of a coactivator to a coactivator binding site on the ligand binding domain is affected.

135. (Previously presented) The method of claim 134 wherein said compound is an antagonist and binding of a coactivator is inhibited.

136. (Currently amended) An isolated and purified protein complex comprising:
an estrogen receptor ligand binding domain;
~~a ligand~~ an agonist bound to the ligand binding domain of the receptor; and
a coactivator bound to a coactivator binding site of the receptor.

137. (Previously presented) The isolated and purified protein complex of claim 136, wherein said coactivator is a peptide that comprises a motif whose sequence is LXXLL, wherein X is any amino acid residue.

138. (Previously presented) The isolated and purified protein complex of claim 137, wherein said coactivator is a GRIP1 peptide.

139. (Previously presented) An isolated and purified polypeptide consisting of a portion of the human estrogen receptor starting at amino acid residue 305 and ending at amino acid residue 549, as set forth in SEQ ID NO: 27 or SEQ ID NO: 28, bound to a ligand, and bound to a coactivator.

140. (Previously presented) A method of identifying a compound that modulates nuclear receptor activity, the method comprising:

screening a test compound in an assay characterized by binding of a test compound to the ligand binding domain of the nuclear receptor, wherein the test compound has been modeled by spatially fitting an atomic model of the test compound into an atomic structural model of a portion of the estrogen receptor ligand binding domain, wherein said atomic structural model comprises atomic coordinates of amino acid residues of the estrogen receptor coactivator binding site and coordinates of a molecule bound to the coactivator binding site, thereby identifying a test compound that modulates nuclear receptor activity.

141. (Previously presented) A method of identifying a compound that modulates estrogen receptor activity, the method comprising:

screening a test compound in an assay characterized by binding of a test compound to the ligand binding domain of the estrogen receptor, wherein the test compound has been modeled by spatially fitting an atomic model of the test compound into an atomic structural model of a portion of the estrogen receptor ligand binding domain, wherein said atomic structural model comprises atomic coordinates of amino acid residues of the estrogen receptor coactivator binding site and coordinates of a molecule bound to the coactivator binding site, thereby identifying a test compound that modulates estrogen receptor activity.

142. (New) The cocrystal of claim 47 wherein the molecule is a peptide that comprises a motif whose sequence is LXXLL, wherein X is any amino acid residue.

143. (New) The cocrystal of claim 47 wherein the molecule is a GRIP1 peptide.

144. (New) The cocrystal of claim 44 wherein the agonist is DES.
145. (New) The cocrystal of claim 44 wherein said cocrystal diffracts with a resolution value less than 3.6 Å.
146. (New) The cocrystal of claim 44 wherein said cocrystal diffracts with a resolution value less than 3.0 Å.
147. (New) The cocrystal of claim 44 wherein said cocrystal diffracts with a resolution value less than 2.4 Å.
148. (New) The isolated and purified protein complex of claim 136, wherein said agonist is DES.